

evidenced by Paul (ed.) Fundamental Immunology, 2nd edition pp.1060-1061 and 1066-1067 [1989].

Applicant hereby amends two paragraphs of the Specification, and Claims 1, 25, 28 and 29, in order to further the prosecution of the present application and Applicant's business interests, yet without acquiescing to the Examiner's arguments. Applicant submits that the amendments do not introduce new matter, and simply correct obvious errors,<sup>1</sup> or rephrase existing matter.<sup>2</sup> Applicant reserves the right to prosecute the original, similar, or broader Claims in one or more future application(s). In addition, none of the amendments to the Claims is intended to narrow the scope of any of the amended Claims within the meaning of *Festo*.<sup>3</sup>

### **THE CLAIMS ARE NONOBVIOUS**

In the Office Action mailed December 19, 2000, the Examiner rejected Claims 1-6 as being unpatentable over Tao and Stevenson, in view of the **uncited** knowledge of one skilled in the art. In particular, the Examiner originally argued that:

"Neither of these references teach 2 or more Ig with different idiotopes. It would have been prima facie obvious to a person of ordinary skill in the art to make a multivalent vaccine with more than one idiotope, as each B cell is known to produce a single species of Ig with a specified idiotope pattern. B cell lymphoma is well known to one of ordinary skill in the art to be a neoplastic condition that results in an abnormal growth and proliferation of B cells which express different idiotypes as a result of the polyclonal nature of the cells."<sup>4</sup>

In the Final Office Action mailed October 19, 2001, the Examiner maintained this rejection of Claims 1 and 3-6, and therein applied this rejection to newly added Claims 25-32. Applicant must respectfully disagree with the Examiner's rejection and argument. Nonetheless, Applicant has amended Claims 1, 25, 28 and 29, in order to further the prosecution of the present application and Applicant's business interests, yet without acquiescing to the

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<sup>1</sup> MPEP 2163.07 II, citing *In re Oda*, 443 F.2d 1200, 170 USPQ 260 (CCPA 1971).

<sup>2</sup> MPEP 2163.07 I, citing *In re Anderson*, 471 F.2d 1237, 176 USPQ 331 (CCPA 1973).

<sup>3</sup> *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, No. 95-1066, 2000 WL 1753646 (Fed. Cir. Nov. 29, 2000).

<sup>4</sup> Office Action mailed December 19, 2000, at paragraph bridging pages 3 and 4.

Examiner's arguments, and while reserving the right to prosecute originally filed and/or similar Claims in the future. In particular, Applicant has amended Claim 1 to recite "are from" and Claims 25, 28 and, 29 to recite a "multivalent" and various discrete combinations of nucleotide sequences encoding Ig V<sub>H</sub> and V<sub>L</sub> regions.

When challenged to provide support for the Examiner's earlier conclusory statements, and to compensate for the lack of teaching in the cited references, the Examiner introduced several pages from a basic immunology textbook ". . . which indicate that one of ordinary skill in the art would have found it obvious to consider B cell lymphomas as being polyclonal."<sup>5</sup> The Examiner's entire argument rests upon the **incorrect** assertion that B cell lymphomas are polyclonal. To this end, the Examiner cited sections of the classic Fundamental Immunology textbook directed to "Clinical Manifestations of HIV Infection," and "The B Cell in AIDS," respectively. Applicant submits that this citation fails to address the presently claimed invention or even the general issue of B cell lymphoma clonality, as it simply teaches that defects in humoral immunity are observed in HIV-infected individuals. In fact, an examination of the **relevant** section (*See*, "Ig Genes in Lymphoid Malignancies" attached hereto at Tab A) of a recent edition of this textbook indicates that:

"Many malignant tumors have been shown to derive from **single** transformed cells that have undergone **clonal** expansion with failure of normal cellular controls. Lymphoid malignancies of the B-lineage provide a classic demonstration of clonality because they derive from cells with unique genetic material (rearranged Ig genes) distinct from the bulk DNA of the same organism. Similarly, analyses of TCR genes have been valuable in establishing clonality of T-cell malignancies. Examination of both gene systems is useful in establishing the lineage of neoplasms that lack characteristic phenotypic markers and in detecting clonal rearrangements as a marker for malignancy; a huge clinical literature has accumulated [Waldmann, *Adv Immunol* 40:247-321 (1987); Korsmeyer, *Adv Intern Med* 33:1-15 (1988); Felix and Poplack, *Leukemia* 5:1015-1025 (1991); and Veronese *et al.*, *Curr Opin Oncol* 8:346-352 (1996)]."<sup>6</sup>

Furthermore, the Specification teaches that although:

"Somatic variants are known to exist within the population of cells comprising certain B-cell tumors (e.g., low grade or follicular B-cell lymphomas). . . these tumors are

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<sup>5</sup> Final Office Action, mailed October 19, 2001, at page 2.

<sup>6</sup> Max, "Immunoglobulins: molecular genetics," in Paul (ed.) Fundamental Immunology, 4th edition, (Lippincott-Raven Publishers, Philadelphia) p. 163 [1999] (emphasis added); attached hereto at Tab A.

clonal at the level of Ig gene rearrangements (including nucleotide sequence at the V-D-J junctions). . ." (Specification, page 52, lines 18-21).

Hence, in contrast to the assertions of the Examiner, a skilled immunologist would be aware that B cell malignancies are essentially monoclonal at the level of Ig gene rearrangements.

Moreover, the MPEP teaches that:

"The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness."<sup>7</sup>

Clearly, Applicant's multivalent vaccine is nonobvious, as the Examiner has assembled all of the elements of the claimed invention only through assumptions **antithetical** to the teachings of the prior art and to the teachings disclosed in the Specification.

Additionally, the Examiner has professed to be skilled in the art, arguing that ". . . the present Examiner in this case also happens to have had experience working in these fields."<sup>8</sup> Whether the Examiner is or is not skilled in the art is irrelevant, as the Examiner is obliged to enter such assertions as an **affidavit** rather than as an unsupported statement.<sup>9</sup> Applicant has previously challenged the Examiner to provide an affidavit in the Response to Office Action mailed December 21, 2000,<sup>10</sup> yet the Examiner has failed to do so. Applicant again requests that the Examiner provide the requisite affidavit.

Importantly, the Federal Circuit has recently ruled that the PTO must support arguments with **substantial** evidence and may not base rejections on belief or opinions of the Office. When faced with similar circumstances, the Federal Circuit has ruled:

"This assessment of basic knowledge and common sense was not based on any evidence in the record and therefore, lacks substantial evidence support . . . With respect to core factual findings in a determination of patentability . . . the Board cannot simply reach conclusions based on its own understanding or experience -- or on its assessment of what would be basic knowledge or common sense. Rather, the Board must point to some concrete evidence in the record in support of these findings."<sup>11</sup>

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<sup>7</sup> MPEP 2145 X. D. 3. citing *In re Hedges*, 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986).

<sup>8</sup> Final Office Action, page 2.

<sup>9</sup> MPEP 2144.03 and 37 C.F.R. 1.104(d)(2).

<sup>10</sup> Response to Office Action mailed December 21, 2000, at page 9.

<sup>11</sup> *In re Zurko*, Fed. Cir., No. 96-1258, 8/2/01.

Clearly, the Examiner has failed to provide any evidence for the polyclonality of B cell lymphoma, and the desire/methods to generate an Ig variable region-based multivalent vaccine.

In fact, as previously brought to the Examiner's attention in the Response to Office Action mailed December 21, 2000, but not addressed in the Final Office Action mailed October 19, 2001, the Stevenson reference **teaches away** from the use of multivalent vaccines for treatment of B cell lymphomas. In particular, Stevenson states and Applicant has previously quoted:

"For certain B cell tumors, such as follicular lymphoma, which may continue to be exposed to the somatic mutation mechanism following neoplastic transformation, a degree of intraclonal mutational heterogeneity is known to occur . . . However, we do not consider that this presents a problem for vaccination for two reasons: first, there was usually a predominant sequence, and second changes in most or all of the idiotypic determinants would be necessary to allow escape of tumor cells from a polyclonal immune attack. For vaccine design we have chosen to assemble the predominant tumor-related sequence. . .<sup>12</sup>"

This teaching, which speaks against the Examiner's obviousness argument, cannot be discounted. The MPEP specifically teaches:

"A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention."<sup>13</sup>"

Thus, one skilled in the art, following the teachings of the cited references, would be led toward the use of monovalent vaccines, as opposed to the multivalent vaccine compositions of the presently claimed invention. Accordingly, Applicant requests that this rejection be withdrawn.

### CONCLUSION

All grounds of rejection of the Final Office Action mailed October 19, 2001 have been addressed. It is respectfully submitted that the invention as claimed fully meets all requirements and that the claims are in condition for allowance. If a telephone interview

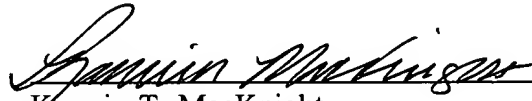
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<sup>12</sup> Stevenson *et al.*, "A genetic approach to idiotypic vaccination for B cell lymphoma," *Annals NY Acad Sci* 772:212-226 [1995]; and Response to Office Action mailed December 21, 2000, at page 10.

<sup>13</sup> MPEP 2141.02, citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

would aid in the prosecution of this application, Applicant encourages the Examiner to call the undersigned collect.

Dated: December 13, 2001



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**APPENDIX I**  
**MARKED-UP VERSION OF REWRITTEN TEXT**  
**PURSUANT TO 37 C.F.R. § 1.121(b)**

Please replace the paragraph beginning on page 88, line 19, with the following text:

The existing approach toward vaccination (*i.e.*, active immunotherapy) of B-cell lymphoma and leukemia involves the production of a custom vaccine comprising autologous immunoglobulin idiotype which corresponds to the most abundant antibody molecule expressed on the surface of the B-cell tumor. An analogous approach for the treatment of T-cell lymphomas and leukemias would involve the production of a custom vaccine comprising autologous T cell receptor (TCR) idiotype which corresponds to the most abundant TCR molecule expressed on the surface of the [B-cell] T-cell tumor.

Please replace the paragraph beginning on page 90, line 8, with the following text:

Two micrograms of pSR $\alpha$ SD7 [(Ex. X)] (Ex. 1) is cut with *SalI* and *HindIII* (NEB enzymes, buffers & conditions). The plasmid is spermine precipitated (Ex. 5) and resuspended in 34  $\mu$ l H<sub>2</sub>O and 4  $\mu$ l of 10x T4 DNA ligase buffer. Equal molar amounts (6.3 ng each) of the unphosphorylated oligonucleotides SXAPH5 (SEQ ID NO:42) and SXAPH3 (SEQ ID NO:43) are added. The reaction is chilled on ice, 400 units of T4 DNA ligase is added and the tube is placed at 14°C overnight. The ligation is transformed into bacteria and clones screened for the presence of the added *AscI* & *PacI* restriction sites. The resulting plasmid is called pSR $\alpha$ SD9. Figure 21 provides a schematic map of pSR $\alpha$ SD9.

**APPENDIX II**  
**MARKED-UP VERSION OF REWRITTEN CLAIMS**  
**PURSUANT TO 37 C.F.R. § 1.121(c)(1)(ii)**

1. (Twice Amended) A multivalent vaccine composition comprising at least two recombinant variable regions of immunoglobulin molecules derived from B-cell lymphoma cells, wherein said at least two variable regions [comprise] are from recombinant immunoglobulin molecules that differ by at least one idiotope.

25. (Amended) A multivalent vaccine composition produced according to a method comprising:

- a) providing:
  - i) malignant B cells isolated from a patient having a B-cell lymphoma;
  - ii) an expression vector;
  - iii) an amplification vector comprising a recombinant oligonucleotide having a sequence encoding a first inhibitable enzyme operably linked to a heterologous promoter; and
  - iv) a T lymphoid parent cell line;
- b) isolating nucleic acid from said malignant cells, said nucleic acid comprising nucleotide sequences selected from the group consisting of nucleotide sequences encoding at least one V<sub>H</sub> region and at least [one] two V<sub>L</sub> [region,] regions, nucleotide sequences encoding at least two V<sub>H</sub> regions and at least one V<sub>L</sub> region, and nucleotide sequences encoding at least two V<sub>H</sub> regions and at least two V<sub>L</sub> regions, wherein said at least two V<sub>L</sub> regions differ by at least one idiotope, wherein said at least two V<sub>H</sub> regions differ by at least one idiotope, and wherein said V<sub>H</sub> and V<sub>L</sub> regions are derived from immunoglobulin molecules expressed by said malignant cells;
- c) inserting said nucleotide sequences encoding said V<sub>H</sub> and V<sub>L</sub> regions into said expression vector;
- d) introducing said expression vector and said amplification vector into said parent cell line to generate one or more transformed cells;
- e) growing said transformed cells in a first aqueous solution containing an inhibitor capable of inhibiting said first inhibitable enzyme wherein the concentration of said

inhibitor present in said first aqueous solution is sufficient to prevent growth of said parent cell line; and

f) identifying a transformed cell capable of growth in said first aqueous solution, wherein said transformed cell capable of growth expresses said  $V_H$  and  $V_L$  regions wherein  $V_H$  and  $V_L$  regions comprise a protein molecule useful as said vaccine.

28. (Amended) A multivalent vaccine composition produced according to a method comprising:

- a) providing:
  - i) malignant B cells isolated from a patient having a B-cell lymphoma;
  - ii) an expression vector;
  - iii) an amplification vector comprising a first recombinant oligonucleotide having a sequence encoding a first inhibitable enzyme operably linked to a heterologous promoter;
  - iv) a selection vector comprising a second recombinant oligonucleotide having a sequence which encodes a selectable gene product; and
  - v) a T lymphoid parent cell line;
- b) isolating nucleic acid from said malignant cells, said nucleic acid comprising nucleotide sequences selected from the group consisting of nucleotide sequences encoding at least one  $V_H$  region and at least [one] two  $V_L$  [region,] regions, nucleotide sequences encoding at least two  $V_H$  regions and at least one  $V_L$  region, and nucleotide sequences encoding at least two  $V_H$  regions and at least two  $V_L$  regions, wherein said at least two  $V_L$  regions differ by at least one idiotope, wherein said at least two  $V_H$  regions differ by at least one idiotope, and wherein said  $V_H$  and  $V_L$  regions are derived from immunoglobulin molecules expressed by said malignant cells;
- c) inserting said nucleotide sequences encoding said  $V_H$  and  $V_L$  regions into said expression vector;
- d) introducing said expression vector, said amplification vector and said selection vector into said parent cell line to generate transformed cells;



- e) introducing said transformed cells into a first aqueous solution, said first aqueous solution requiring the expression of said selectable gene product for growth of said transformed cells;
- f) identifying at least one transformed cell capable of growth in said first aqueous solution;
- g) introducing said transformed cell capable of growth in said first aqueous medium into a second aqueous solution, said second aqueous solution comprising an inhibitor capable of inhibiting said first inhibitable enzyme, wherein the concentration of said inhibitor present in said second aqueous solution is sufficient to prevent growth of said parent cell line; and
- h) identifying at least one transformed cell capable of growth in said second aqueous solution, wherein said transformed cell capable of growth expresses said  $V_H$  and  $V_L$  regions wherein said  $V_H$  and  $V_L$  regions comprise a protein molecule.

29. (Amended) A multivalent vaccine composition produced according to a method comprising:

- a) providing:
  - i) malignant B cells isolated from a patient having a B-cell lymphoma;
  - ii) an expression vector;
  - iii) an amplification vector comprising a first recombinant oligonucleotide having a sequence encoding a first inhibitable enzyme operably linked to a heterologous promoter;
  - iv) a selection vector comprising a second recombinant oligonucleotide having a sequence which encodes a selectable gene product; and
  - v) a T lymphoid parent cell line;
- b) isolating nucleic acid from said malignant cells, said nucleic acid comprising nucleotide sequences selected from the group consisting of nucleotide sequences encoding at least one  $V_H$  region and at least [one]  $V_L$  [region,] regions, nucleotide sequences encoding at least two  $V_H$  regions and at least one  $V_L$  region, and nucleotide sequences encoding at least two  $V_H$  regions and at least two  $V_L$  regions, wherein said at least two  $V_L$  regions differ by at least one idiotope, wherein said at least two  $V_H$  regions differ by at least one idiotope, and

wherein said  $V_H$  and  $V_L$  regions are derived from immunoglobulin molecules expressed by said malignant cells;

c) inserting said nucleotide sequences encoding said  $V_H$  and  $V_L$  regions into said expression vector;

d) introducing said expression vector, said amplification vector and said selection vector into said parent cell line to generate transformed cells;

e) introducing said transformed cells into a first aqueous solution, said first aqueous solution requiring the expression of said selectable gene product for growth of said transformed cells;

f) identifying at least one individual clone of transformed cells capable of growth in said first aqueous solution;

g) introducing said individual clone capable of growth in said first aqueous solution into a second aqueous solution, said second aqueous solution comprising an inhibitor capable of inhibiting said first inhibitable enzyme, wherein the concentration of said inhibitor present in said first aqueous solution is sufficient to prevent growth of said parent cell line; and

h) identifying at least one individual clone capable of growth in said second aqueous solution, wherein said clone capable of growth expresses said  $V_H$  and  $V_L$  regions wherein said  $V_H$  and  $V_L$  regions comprise a protein molecule.

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# FUNDAMENTAL IMMUNOLOGY

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